Published in final edited form as:

Annu Rev Pharmacol Toxicol. 2019 January 06; 59: 149–170. doi:10.1146/annurev-pharmtox-010818-021358.

Fingolimod: Lessons Learned and New Opportunities for Treating Multiple Sclerosis and Other Disorders

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Abstract

Fingolimod (FTY720, Gilenya) was the first US Food and Drug Administration–approved oral therapy for relapsing forms of multiple sclerosis (MS). Research on modified fungal metabolites converged with basic science studies that had identified lysophospholipid (LP) sphingosine 1-phosphate (S1P) receptors, providing mechanistic insights on fingolimod while validating LP receptors as drug targets. Mechanism of action (MOA) studies identified receptor-mediated processes involving the immune system and the central nervous system (CNS). These dual actions represent a more general theme for S1P and likely other LP receptor modulators. Fingolimod's direct CNS activities likely contribute to its efficacy in MS, with particular relevance to treating progressive disease stages and forms that involve neurodegeneration. The evolving understanding of fingolimod's MOA has provided strategies for developing next-generation compounds with superior attributes, suggesting new ways to target S1P as well as other LP receptor modulators for novel therapeutics in the CNS and other organ systems.

Keywords

GPCRs; lysophospholipids; LPA; S1P; FTY720; Gilenya; neurodegeneration; drugs; medicines

INTRODUCTION

The entry of fingolimod (FTY720, Gilenya) (1–6) into clinical practice as the first oral treatment for relapsing forms of multiple sclerosis (MS) (7, 8) represented a milestone for both the treatment of MS and the mechanistic relevance of lysophospholipid (LP) receptors (9) as bona fide therapeutic targets (10) through the LP receptor branch containing sphingosine 1-phosphate (S1P) receptors. This review highlights the tortuous yet instructive path that led to fingolimod's clinical success. Fingolimod's development portends future success with multiple next-generation agents in relapsing and progressive forms of MS and possibly other central nervous system (CNS) and non-CNS therapeutic areas. This review cannot be fully comprehensive, and other important information can be found in an extensive primary literature and previously published reviews (11–14).

MS is the most common cause of demyelination and neurological disability in young adults (15, 16) and is associated with a broad range of CNS dysfunction. In its most common form,

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relapsing remitting multiple sclerosis (RRMS), MS is generally thought to arise through nervous system damage initiated by the immune system (although the initiating causes remain unknown), where it manifests as attacks interspersed with periods without symptoms involving subclinical disease that continues to produce brain damage (15). Not uncommonly, RRMS can lead to a state of progressive disability without remission known as secondary progressive multiple sclerosis (SPMS) (16). A rare form that is thought to be less reliant on immunological insult and that also progresses is primary progressive multiple sclerosis (PPMS) (16). All forms have neurodegeneration and the resultant disability as their most serious sequelae. The last 15 years have seen a dramatic increase in new disease-modifying therapies (DMTs) for MS (17), which arguably has the most new therapies of any CNS disorder.

Fingolimod's actions in MS became mechanistically understood through the parallel discovery of LP receptors (9, 18–21). The historical background behind LP receptors and FTY720/fingolimod, along with basic science and clinical data in the immune system and CNS, provides illustrative lessons on the path that enabled fingolimod to enter clinical practice. These experiences are relevant to what might be encountered in both the current and future development of LP receptor modulators, with implications for understanding the brain and its diseases, as well as disorders affecting other parts of the body.

LYSOPHOSPHOLIPID RECEPTORS

The molecular mechanisms for lipid effects have been challenging to identify, and researchers encountered mechanistic ambiguity for both of the best-studied LPs, lysophosphatidic acid (LPA) and S1P, as well as other LPs and fingolimod (discussed below). Erroneous identifications precluded or slowed mechanistic understanding and rational drug development. For illustrative purposes, some background on LP receptors is provided in this review, with further details available in prior reviews (9, 10, 18–20, 22–26).

LPs are derived from membrane phospholipids and sphingolipids that were first isolated from brain in the nineteenth and early twentieth centuries and include glycerophospholipids (27, 28), like LPA (29, 30), and sphingosine-containing phospholipids (28, 31), like S1P (32, 33) (Figure 1). In addition to their early-recognized lytic properties accounting for their name (29, 30), exogenously applied LPs were found to produce a range of effects, including changes in blood pressure (34) and cell physiology (35, 36). However, the molecular mechanisms for these effects were unclear through the early 1990s, with explanations ranging from their action as detergents (37) to their function as calcium ionophores (38), second messengers (39), and intracellular receptors (40, 41) as well as circumstantial evidence for LPA and S1P being G protein–coupled receptors (GPCRs) (42, 43). The first molecularly characterized LP receptor, the GPCR LPA1 (44), was identified from studies of the brain [it was called ventricular zone gene 1 (*VZG-1*) at the time for its expression in this neurogenic CNS region] (44–46), and it mediated the actions of LPA. Its complementary DNA sequence enabled deorphanization of homologous receptor genes, which were known by multiple orphan receptor names at the time (47), particularly EDG (20, 48), leading to additional receptors for both LPA (49, 50) and S1P (51, 52).

The confirmation and acceptance of LP receptor identities required years of research and were challenged by frank skepticism (53, 54), confusion over ligand identities (55), and multiple prominent reports that misidentified LP receptors (56–61). The advent of receptor heterologous expression approaches (45), receptor knockout mice (46, 62), new reporter systems (63), and receptor-selective chemical tools (10, 22, 26, 64) has clarified LP receptor identities within the superfamily of GPCRs, which now also includes sequence-dissimilar LPA, lysophosphatidyl inositol/glucose (65, 66), and lysophosphatidyl serine (63) receptors, totaling 15 class A GPCRs identified thus far (Figure 2). Most have been knocked out in mice (46, 62, 67–77), revealing a vast range of biology and pathophysiology (78). All LP receptors signal through heterotrimeric G proteins to activate a broad range of downstream signaling pathways (Figure 3), and the crystal structures of S1P1 (79), LPA1 (80), and LPA6 (81) have been reported. An additional element impacting lipid signaling is their presentation to receptors by protein chaperones (82, 83).

This brief history underscores the need to validate molecular mechanisms, which enabled the development of fingolimod and continues to enable the pursuance of next-generation agents directed at multiple medically important areas. The level of research activity in the LP receptor field was unquestionably elevated by the realization that FTY720, through its phosphorylated metabolite FTY720-P, engaged lysophospholipid S1P receptors (84, 85). However, this receptor mechanism was published seven years after the publication of FTY720 (86, 87), meaning that the pre clinical studies, including chemical modifications (88) and early clinical development, occurred in the absence of known target receptors and mechanisms of action (MOAs).

FTY720 AS AN IMMUNOSUPPRESSIVE AGENT IN TRANSPLANTATION

Pharmaceutical studies in Japan on the entomopathogenic Ascomycota fungus *Isarii sinclarii* (Figure4a,b) identified fungal metabolites with immunosuppressive properties. One such product was ISP-1 (87, 89–92), which had been identified 20 years earlier from other fungi and was used as an antibiotic called myriocin (93) or thermozymocidin (94) (Figure 4c). Chemical modifications of myriocin to reduce toxicity in animal models (11, 86) led to FTY720 (14, 86, 92, 95) (Figure 4c). Early preclinical work implicated FTY720 as a cytotoxic, immunosuppressive agent that killed lymphocytes, particularly $CD4^+$ T cells, via an unknown molecular mechanism (86, 96–98), which could be useful in preventing the rejection of allograft organ transplantation and treating autoimmune diseases (95, 99). Myriocin was shown to inhibit serine palmitoyltransferase (Figure 5) (*SPTLC1/2/3*), which FTY720 did not, and led to the recognition that sphingolipids, including S1P, could be relevant to fingolimod's activity (89). Yet all of these studies occurred before widespread recognition of both the existence of LP receptors and their linkage to FTY720. Biologically driven activity screens in animal models and a mixed lymphocyte reaction assay (87) that reported lymphocyte proliferation and apoptosis (96, 97, 100–102) led to the conclusion that FTY720 was a strong immunosuppressive agent that induced cytotoxicity. Indeed, in a rat skin allograft model, FTY720 was reported to show 30-fold higher immunosuppressive activities than cyclosporine A (95), raising the possibility of replacing cyclosporine or combining it with lower doses of FTY720. Other cellular mechanisms, particularly lymphocyte sequestration, were also identified in later studies (103, 104). These properties

resulted in FTY720 being licensed by Yoshitomi and its successors (now Mitsubishi Tanabe) and Novartis (previously Ciba-Geigy/Sandoz) for use in renal transplantation (14).

FTY720 was pursued clinically as a novel immunosuppressive agent suitable for reducing rejection in organ transplantation based on multiple animal models, including renal transplantation (105–107). These animal studies included data showing FTY720 was much more potent than cyclosporine A, yet with fewer side effects (11), and could allow reduced cyclosporine dosing (108). Researchers pursued clinical development (11, 109–111), including two phase III trials in de novo renal transplantation. However, trial results demonstrated a lack of superiority compared to conventional agents, decreased renal function, and increased adverse events (109–111).Notably, high-dose (5mg) FTY720 combined with reduced-dose cyclosporine did not reach its primary end point (111), a surprising result in light of prior FTY720 potency data (95). A lack of superiority under any dosing regimen, combined with a range of adverse events affecting not only renal function but also the heart, lungs, and eyes, halted further development at the time (109).

Reasons for the discrepancies between promising transplantation animal studies and human data are unclear but might reflect species differences, although positive animal signals in multiple models were observed in both rats (96, 99, 102) and dogs (102, 107). Experimental paradigms that initially reported cytotoxicity (96, 97, 112) but later lymphocyte sequestration (103, 104, 113)—generally, the current immunological MOA for fingolimod in MS—may have obfuscated the predominantly nonimmunosuppressive features of FTY720. For example, assayed drug concentrations ranged 300-fold for experimental animal dosing (86) from 0.1 mg/kg to 30 mg/kg, the latter of which would be 4,200 times the approved dose for fingolimod in MS (0.5 mg for a 70-kg patient) (7, 8) and which could have accessed different cytotoxic mechanisms. The adverse event profile was notable for its occurrence in transplant patients exposed to a combination of cyclosporine (mostly at accepted immunosuppressing concentrations) simultaneously with fingolimod in amounts up to 10 times the currently approved dose for MS. The relevance of these safety signals to those anticipated in an entirely different MS patient population receiving fingolimod monotherapy at much lower doses is debatable (discussed further below). All of these studies were conducted in the absence or nascence of knowledge about S1P receptor mechanisms. However, emerging data on the actual receptor mechanisms of FTY720 combined with signals in animal models of MS suggested alternative clinical uses.

FINGOLIMOD (GILENYA) FOR MULTIPLE SCLEROSIS

Basic science studies on the MOA for FTY720 identified the phosphorylated metabolite FTY720P as a receptor agonist for multiple S1P receptor subtypes (S1P1,3,4,5) (84, 85). This receptor identity suggested alternative clinical uses for FTY720 involving the immune system, in view of the lymphocyte and transplantation data (103, 112), and especially the brain, from which the first LP receptor had been identified (44). Indeed, LP receptors (for LPA and/or S1P)were known to be expressed in most major cell types within the nervous system (114–116), including astrocytes (117, 118), neuroprogenitor cells (44, 119), neurons (46, 120), myelinating glia (121–123), microglia (124), and endothelial cells (48, 119), all of which are relevant in MS. Animal studies from multiple groups using experimental

autoimmune encephalomyelitis (EAE), a widely used animal model of MS, identified efficacy signals where in FTY720 could prevent EAE clinical disease (84, 125). This result was not surprising in view of the dependence of pathogenic T cell entry into the CNS (126, 127), as is also observed for non-CNS models (128), which was reduced by FTY720. Critically, the therapeutic effects of FTY720 administered after the onset of disease were also documented (129), which further supported the use of FTY720 in MS. A proof-of-concept phase II study demonstrated efficacy as a monotherapy in MS (1) at transplant dosing levels (1.25 and 5 mg). Subsequent phase III studies employed lower doses (0.5 and 1.25 mg) that demonstrated superiority versus a placebo (6) or versus interferon β−1a (5) in relapsing forms of MS, which provided sufficient data for US Food and Drug Administration (FDA) approval of fingolimod as a first-line agent at the 0.5 mg dose in September 2010 (13).

Efficacy signals were found in both phase III trials and included improvements in disability progression in the placebo trial, which is a surrogate for reducing neurodegenerative sequelae (6, 7), thus supporting the advantageous properties of S1 Preceptor modulation. The extensive list of side effects, which were encountered in renal transplantation studies with concomitant cyclosporine A immunosuppression at 10 times the MS-approved dose, led to their assessment in MS trials. Notably, signals detected in transplantation studies and the nevaluated in the very different setting of MS resulted in the detection of rare subclinical or asymptomatic signals (e.g., asymptomatic bradycardia) (7). This raises questions as to the most appropriate approach to monitoring safety signals that provide a true and accurated escription of anagent’s safety liabilities given its level of efficacy (i.e., more efficacious agents may be accompanied by more possible toxicities). An interesting, though unfeasible, trial would be to examine other approved MSDMTs under conditions of cyclosporine immunosuppression at 10 times their currently approved dose to identify possible adverse events and then to search actively for the same adverse reactions again at the approved dosing. Undoubtedly, more adverse events would be identified in both circumstances, and then the events could be contrasted with postmarketing experiences, which could point to truly meaningful safety signals. For fingolimod, this raises the additional question of how to identify the lowest effective dose, which relates to mechanism (discussed below).

IMMUNOLOGICAL MECHANISMS OF FINGOLIMOD

A key effect of fingolimod in MS is its reduction of peripheral blood lymphocytes, particularly T cell subtypes, which had been observed both in early preclinical studies (85, 103, 104, 113) and in clinical trials (1, 5, 6, 130). The reduction is not due to cytotoxicity, as first envisaged, but rather to lymphocyte sequestration in secondary lymphoid organs (13, 14, 85, 103, 131) produced by the direct receptor-mediated effects of phosphorylated fingolimod, which results in perturbed lymphocyte traffic king and egress out of lymphnodes and in to the periphery. Paradoxically, despite the originally identified S1 Preceptor agonism (84, 85) produced by fingolimod-phosphate, it is the loss of receptor activity by functional antagonism, involving irreversible receptor internalization and degradation, particularly S1P1 (132) (Figure 6), that accounts for fingolimod’s effects on lymphocyte traffic king where by pathogenic cells entering the CNS are reduced. T cells appear to be the most prominently affected, with differential effects whereby naïve and central memory T cells are

sequestered, but some effect or and effect or memory cells are not (13, 14, 133), and there appear to be intermediate effects on B cells (134) and at least some cells of the innate immune system [e.g., natural killer cells (73)].

These differential effects offer a feasible explanation for the proposed immune-related efficacy signals in MS through the sequestration of pathogenic T cell subsets, and they also explain the inability of fingolimod to act as a major immunosuppressive agent because of maintained immune surveillance by the effect or lymphocyte population subsets and other cell types of the innate immune system. The latter non immune suppressive activities manifest in two ways. First, FTY720 failed to show superiority in renal transplantation despite the combination of a high dose of FTY720 with a full dose of cyclosporine, and it showed inferiority when used adjunctively with a reduced cyclosporine dose (111). Second, fingolimod did not produce a major mechanism-based opportunistic infection signal. Infection signals do exist, however, not at the levels encountered with prolonged, frank immunosuppression. For example, the rates of progressive multifocal leukoencephalopathy (caused by JC virus infection) in immunosuppressed individuals, as is encountered with untreated HIV (2.4per1,000) (135) or natalizumab treatment (between1–10per1,000) (136), exceed by over ten fold the rates observed with fingolimod exposure (<0.1per1,000) (136). Clearly, the mechanism through which fingolimod alters immune function is not immunosuppressive as compared to cyclosporine A or natalizumab (137, 138), yet it attains comparable efficacy in MS.

Accumulating data support stratifying MS patients into those who may respond better and/or encounter fewer adverse events on fingolimod and related S1P receptor modulators and those who may not. For example, significantly better efficacy responses have been observed in younger MS patients (designated a breakthrough therapy for pediatric MS by the FDA) (139), and in general, fewer adverse events relative to efficacy end points have been encountered in younger, less medically complicated patients, as epitomized by results in a phase III multiple sclerosis pediatric clinical trial (PARADIGMS) (140). The immunological mechanisms of fingolimod likely have important roles in reducing a primary end point in clinical trials, the annualized relapse rate (ARR) (5, 130), but do not appear to be the only mechanism accessed by fingolimod, implicating additional mechanisms beyond immunomodulation, as discussed next.

CENTRAL NERVOUS SYSTEM MECHANISMS OF FINGOLIMOD

Functional signals from both the clinical literature and animal studies support additional, nonimmunological mechanisms accessed by fingolimod. Its effects on lymphocyte trafficking (141, 142) included a dose-responsive reduction of peripheral blood lymphocytes with increasing doses of fingolimod in humans (143). However, fingolimod efficacy in phase III MS clinical trials showed the reverse relationship, with increased efficacy at the lower (0.5mg versus 1.25mg) fingolimod doses affecting multiple clinical end points (5, 6), including a primary end point of ARR (5). These data demonstrated a discordance between lymphocyte level sand fingolimod efficacy in MS, which was independently consistent with discordant lymphocyte levels and clinical disease scores observed in earlier animal models (129). The widespread expression of S1Preceptors within the CNS (14) (see above),

combined with the preferential location of administered FTY720 (in animal models) within the CNS (144), demonstrated that the direct actions of fingolimod are beneficial in MS.

Experimental evidence for direct CNS activities (131, 133, 145–148) has revealed a large range of different physiological responses that are relevant to fingolimod actions in MS. These responses are distinct from immunological effects and span experimental systems from cell culture and primary cells to animal models. The CNS cell types that fingolimod acts on include astrocytes (75, 118, 149, 150), oligodendrocytes and their precursors (151, 152), neurons and progenitors (14, 153–155), microglia (131, 156, 157), and cells of the blood-brain barrier (158–160). Of particular note, mice selectively deficient for S1P1 in astrocytes but not other neural or immune cell types showed reduced EAE disease severity and CNS damage to myelin and neurons (75). Moreover, astrocyte S1P1 loss eliminated fingolimod efficacy despite the maintenance of expected effects on lymphocyte trafficking (Figure 7), which provides experimental support for direct CNS mechanisms through astrocyte S1P1. These and other studies are part of an expanding literature identifying the direct CNS effects of fingolimod (Figure 8) and other S1P receptor modulators in model systems that support similar mechanisms to those occurring in MS. Indeed, multiple lines of clinical data are consistent with direct CNS activities in human disease, as discussed below.

Imaging studies in MS patients under treatment with natalizumab versus fingolimod report opposite effects on brain volume preservation despite both being thought to share similar MOAs by preventing pathogenic lymphocytes from entering the CNS. Natalizumab (and interferons, another MS treatment) produces brain volume loss (called pseudoatrophy) (161, 162), in contrast with fingolimod treatment, which preserves brain volume (5, 6) that has been linked to functional preservation (163). Brain volume preservation has also been observed with the next-generation S1 Preceptor modulator siponimod (BAF312) that showed positive results for multiple end points, including brain volume preservation in SPMS (164). Although fingolimod testing in PPMS did not reach the desirable functional end points, these negative data occurred in the absence of brain volume preservation (148, 165), suggesting a PPMS disease state that was too advanced for fingolimod efficacy, which is analogous to ineffectual DMT trials in Alzheimer’s disease that are now examining earlier disease stages (166). Independent human data supporting direct CNS target engagement by fingolimod may be seen through fingolimod exacerbation of neuromyelitis optica, a disease distinct from MS that involves aquaporin-4 on astrocytes (167), consistent with astrocyte S1P1 receptor engagement. Combined with the discordance between peripheral blood lymphocyte levels that decrease with increasing fingolimod on one hand and the improved MS efficacy with decreased fingolimod dosing on the other, the clinical picture is consistent with direct CNS activities identified experimentally in model systems. Direct CNS mechanisms support the possibility of a lower effective dose that could also allow for improved safety. The existence of the CNS mechanisms of fingolimod indicates the future potential of this drug in other brain disorders involving neurodegenerative processes such as stroke (168).

NEXT-GENERATION LYSOPHOSPHOLIPID RECEPTOR MODULATORS AND DISEASES

Validated S1P receptor mechanisms in MS accessed by fingolimod have provided an impetus for next-generation agents with receptor selectivity that could have superior properties—in efficacy and/or safety—in relapsing and progressive forms of MS, as well as beyond MS. It is notable that adverse events increase with increasing fingolimod doses, which could reflect the increased engagement of the responsible S1P receptor subtypes on a variety of relevant cell types; the production of receptor-selective compounds could avoid such liabilities. More broadly, fingolimod has also provided proof-of-concept support for other LP receptors as drug targets. Chemical entities that have entered human clinical trials (Figure 9) include both S1P and LPA receptor modulators. Beyond fingolimod, a range of primarily autoimmune diseases have been targeted, including RRMS (ozanimod, siponimod, ponesimod, ceralifimod, GSK-2018682), SPMS (siponimod), psoriasis (ponesimod), lupusery the matosus (mocravimod), malignancies (mocravimod), and inflammatory bowel disease (etrasimod, mocravimod). LPA1 antagonists are being examined in fibrotic diseases such as idiopathic pulmonary fibrosis (BMS-986020)and systemic sclerosis (SAR100842). Of particular note are the positive phase III trial data for siponimodin SPMS (164) that may not have been anticipated from a purely immunological MOA, but that would be consistent with direct CNS activities. Patient selection for appropriate disease states in PPMS may auger future successes by one or more S1P receptor modulators, including siponimod and fingolimod. Further clarification of the MOAs could optimize effective dosing to reduce adverse events. Other diseases and organ systems could be accessed by LP receptor modulators (Figure 10)(78), and it is certain that new medicines will emerge through the therapeutic modulation of this growing family of receptors.

CONCLUDING REMARKS

Research on fingolimod and LP receptors has synergized to open new vistas on basic biology, diseases, and therapeutics. Clearly, a rigorous understanding of the correct receptor mechanisms accessed by fingolimod was important to its successful entry into the medicinal armamentarium and essential for developing next-generation therapeutics, underscoring the benefit of obtaining this knowledge. Failure in one therapeutic area does not rule out success in another, as was the case for fingolimod, but it may require creative approaches in considering and handling efficacy and safety variables. Matching drug attributes with optimal patient characteristics could improve both efficacy and safety for a given agent, as is now apparent for fingolimod. The development of future LP receptor medicines can build on this experience to create new therapeutics for the brain and other organ systems.

ACKNOWLEDGMENTS

The authors would like to thank Christian Munk for supplying the GPCR phylogenetic data in Figure 2. This work was supported by the National Institutes of Health (NS084398 to J.C. and NS103940 to Y.K.), the US Department of Defense (W81XWH-17-1-0455 to J.C.), and the American Heart Association (16SDG27020014 to V.A.B.).

DISCLOSURE STATEMENT

J. C. has received consulting fees or research support from Abbott, AbbVie, Amira, Arena Pharmaceuticals, Biogen-IDEC, Bioline RX, Blade Therapeutics, Brainstorm Cell Therapeutics, Celgene, GlaxoSmithKline, Inception Sciences, Johnson & Johnson, Merck, Mitsubishi Tanabe, Novartis, Ono Pharmaceuticals, Pfizer, Skai Ventures, and Taisho Pharmaceutical Co.

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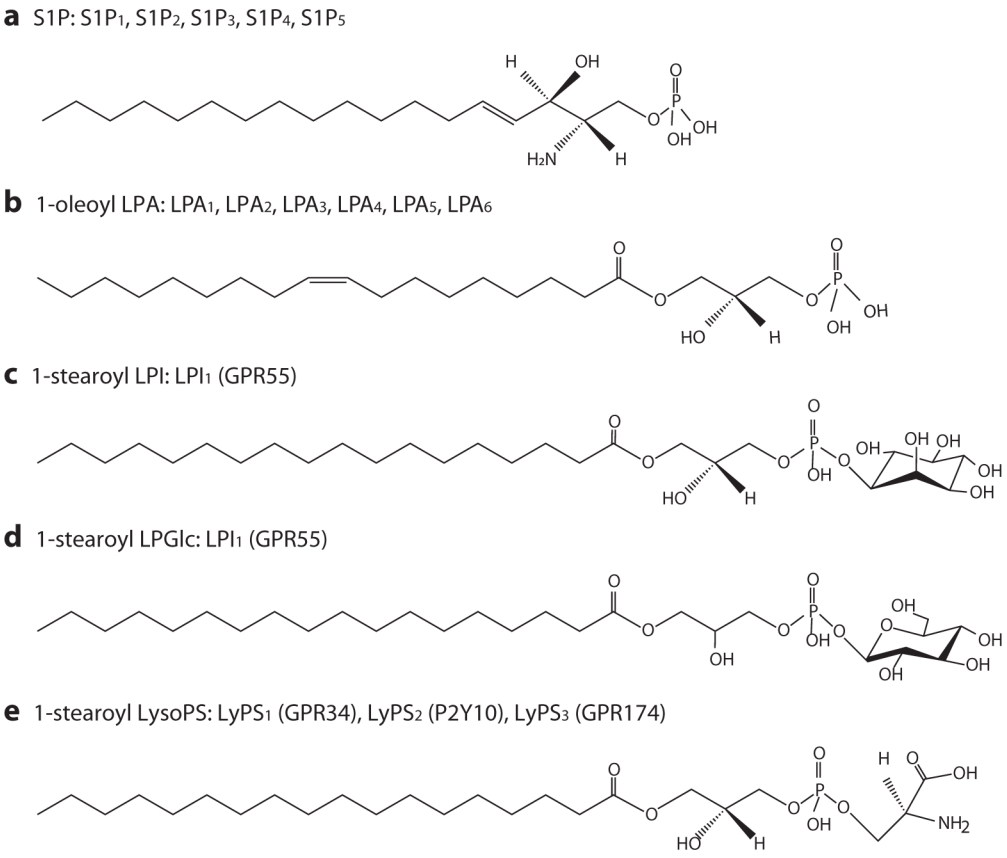

Figure 1.

Chemical structures of LPs, showing their chemical names and receptors. IUPAC names for each of the LPs are as follows: (*a*) S1P, [(*E*,2*S*,3*R*)-2-amino-3-hydroxyoctadec-4-enyl] dihydrogen phosphate; (*b*) 1-oleoyl LPA, (2-hydroxy-3-phosphonooxypropyl) (*Z*)-octadec-9-enoate; (*c*) 1-stearoyl LPI, [(2*S*)-2-hydroxy-3-[hydroxy-[(2*R*,3*R*,5*S*,6*R*)-2,3,4,5,6-pentahydroxycyclohexyl] oxyphosphoryl]oxypropyl] octadecanoate; (*d*) 1-stearoyl LPGlc, 2-hydroxy-3-phosphonooxypropyl[6-(hydroxymethyl)oxane-3,4, 5-triol] octadecanoate; and (*e*) 1-stearoyl LysoPS, (2*S*)-2-amino-3-[hydroxy-[(2*R*)-2-hydroxy-3-octadecanoyloxypropoxy]phosphoryl] oxypropanoic acid. Abbreviations: IUPAC, International Union of Pure and Applied Chemistry; LP, lysophospholipid; LPA, lysophosphatidic acid; LPGlc, lysophosphatidyl glucose; LPI, lysophosphatidylinositol; LysoPS, lysophosphatidyl serine; S1P, sphingosine 1-phosphate.

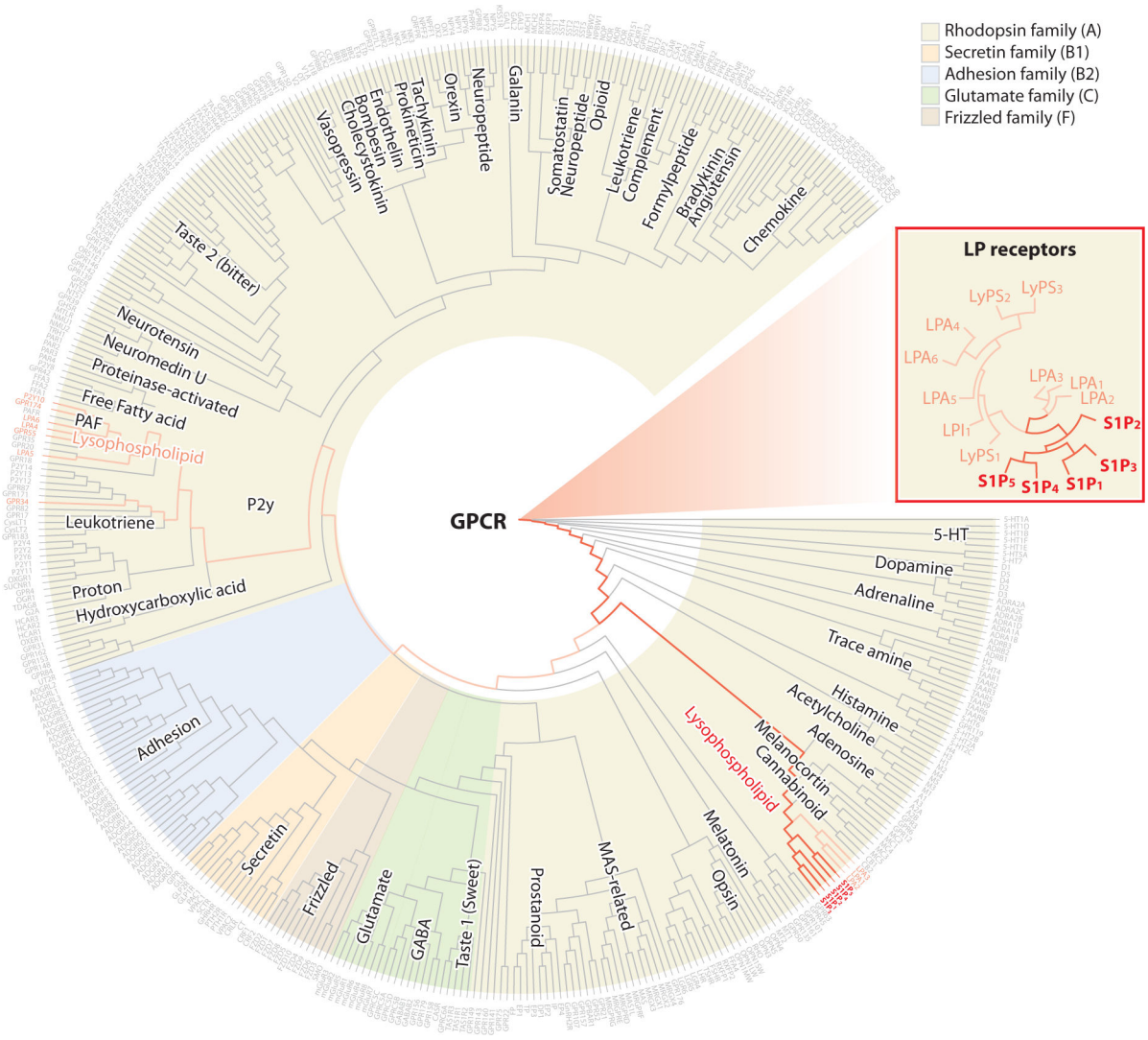

Figure 2.

A phylogenetic tree of human GPCRs and LP receptors. GPCRs are classified into five families: rhodopsin, secretin, adhesion, glutamate, and frizzled. LP receptors belong to the rhodopsin family, while newly identified LP receptors (LPA_4, LPA_5, LPA_6, LPI_1/GPR55, $LyPS_1$/GPR34, LyPS2/P2Y10, LyPS3/GPR174) are phylogenetically distant from members of the classical EDG receptor family ($S1P_1$/EDG-1, $S1P_2$/EDG-5, $S1P_3$/EDG-3, $S1P_4$/EDG-6, $S1P_5$/EDG-8, LPA1/EDG-2, LPA2/EDG-4, and LPA3/EDG-7). Abbreviations: GPCR, G protein–coupled receptors; LP, lysophospholipid; LPA, lysophosphatidic acid; S1P, sphingosine 1-phosphate.

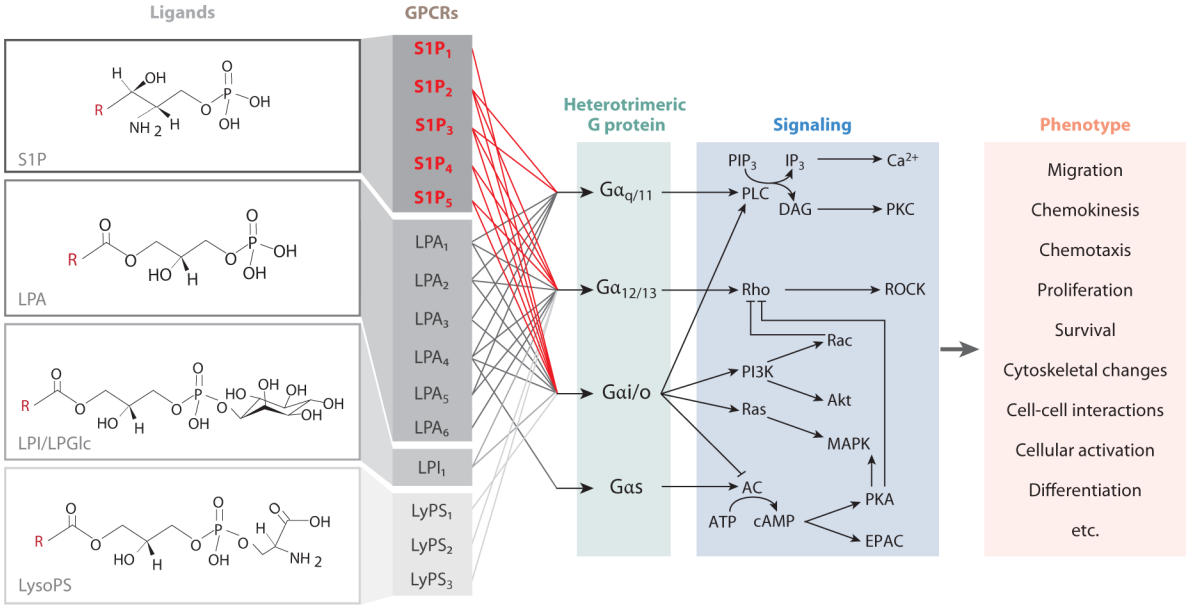

Figure 3.

LP receptor signaling. LPs activate their specific receptors, which transduce signals through heterotrimeric Gα proteins (Gαq/11, Gα12/13, Gαi/o, Gαs), followed by the activation of various intracellular signaling molecules: PIP2, IP3, PLC, DAG, PKC, Rho, ROCK, PI3K, Rac, MAPK, AC, ATP, cAMP, PKA, and EPAC. The five S1P receptor subtypes are highlighted in red. Abbreviations: AC, adenylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; EPAC, exchange protein directly activated by cAMP; GPCR, G protein–coupled receptors; IP3, inositol trisphosphate; LP, lysophospholipid; LPA, lysophosphatidic acid; LPGlc, lysophosphatidyl glucose; LPI, lysophosphatidylinositol; LysoPS, lysophosphatidyl serine; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; Rac, ras-related C3 botulinum toxin substrate; Rho, ras homolog gene family; ROCK, Rho kinase; S1P, sphingosine 1-phosphate.

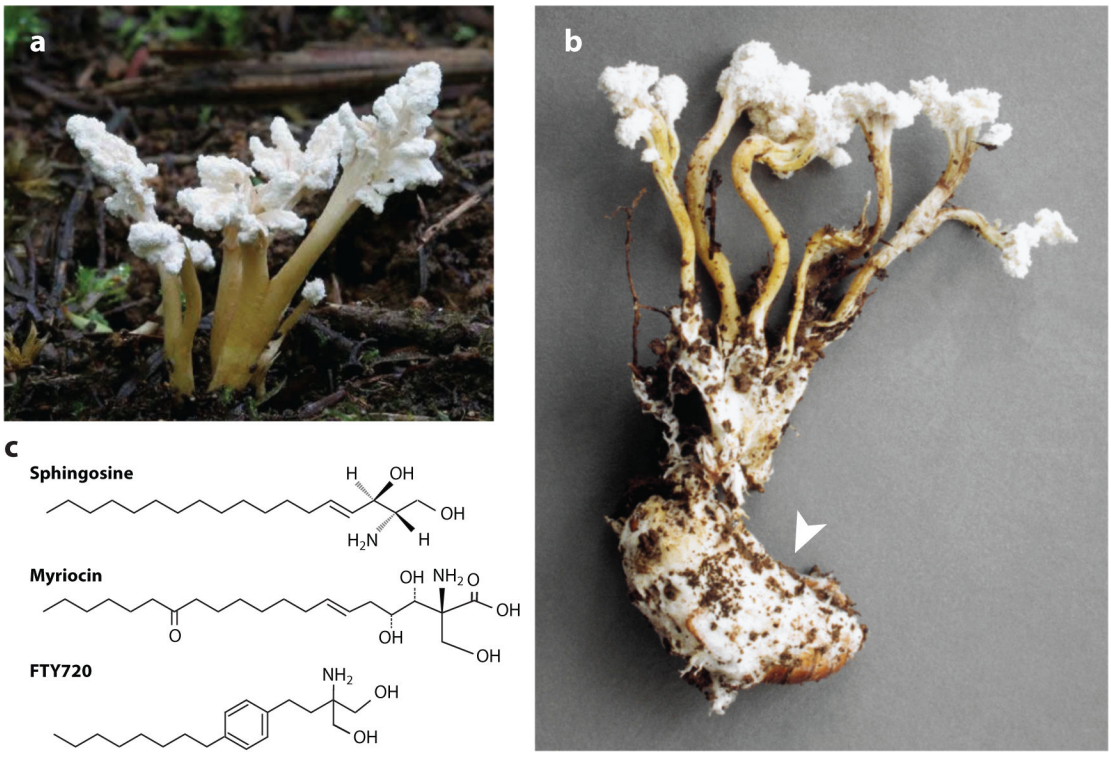

Figure 4.

Origin of fingolimod. (*a*) Wild cordyceps (Isaria sinclairii, phylum Ascomycota), which is also called winter worm, summer grass. (b) The intact cordyceps fungus with host insect carcass (*white arrow*). (c) Chemical structure of sphingosine, myriocin, and FTY720. The IUPAC names of these compounds are as follows: sphingosine, (*E,2S,3R*)-2-aminooctadec-4-ene-1,3-diol; myriocin (ISP-1), (*E,2S,3R,4R*)-2-amino-3,4-dihydroxy-2-(hydroxymethyl)-14-oxoicos-6-enoic acid; and FTY720, 2-amino-2-[2-(4-octylphenyl)ethyl] propane-1,3-diolhydrochloride. Abbreviation: IUPAC, International Union of Pure and Applied Chemistry. Panels a and b reproduced with permission from Clive Shirley (http://hiddenforest.co.nz/fungi/index.htm).

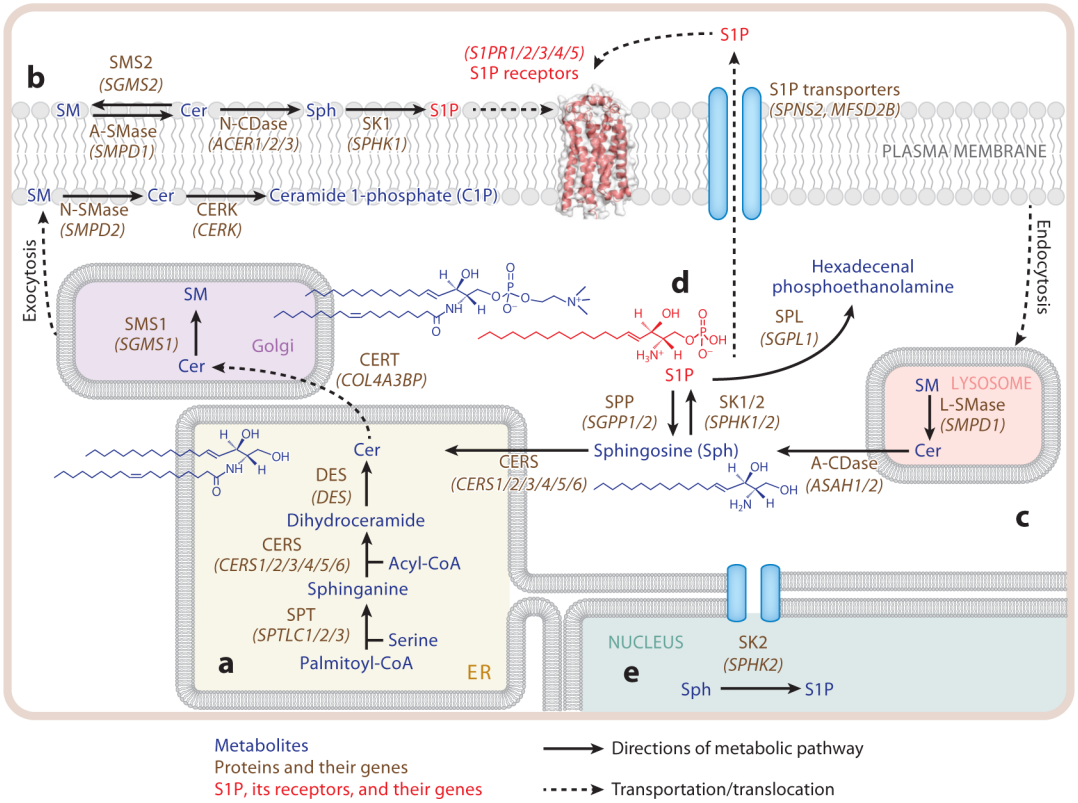

Figure 5.

Sphingolipid and S1P metabolism. (*a*) The beginning of de novo sphingolipid biosynthesis is a sequential action of SPT and 3-ketosphinganine reductase, which produces sphinganine (dihydrosphingosine). CERS produce a variety of dihydroceramides consisting of various lengths of fatty acyls, followed by the reduction of dihydroceramide to Cer by DES. Cer generated in the ER is transported to the Golgi apparatus by CERT. The choline group is transferred from phosphatidylcholine to Cer by SMS, generating SM. (*b*) Production of S1P by the salvage pathway begins when Cer is produced at the plasma membrane by the action of sphingomyelinases (A-SMase, N-SMase), which in turn is converted to Sph by ceramidase (N-CDase). SK1 phosphorylates sphingosine-generating S1P. (*c*) L-SMase and A-CDase degrade complex sphingolipids into sphingosine via the endolysosomal pathway. In the sphingosine salvage pathway, Cer is generated from free sphingosine by CERS. (*d*) SK1 and SK2 generate S1P, which is exported via the S1P transporter SPNS2 or MFSD2B. S1P is metabolized to sphingosine by SPP or degraded to hexadecenal and phosphoethanolamine by SPL. (e) S1P is also generated in the nucleus by SK2. Abbreviations: A-CDase, acid CDase; A-SMase, acid SMase; Cer, ceramide; CERK, ceramide kinase; CERS, ceramide synthases; CERT, ceramide transport protein; DES, dihydroceramide desaturase; ER, endoplasmic reticulum; L-SMase, lysosomal acid SMase; MFSD2B, major facilitator superfamily domain containing 2B; N-CDase, neutral CDase; N-SMase, neutral SMase; S1P, sphingosine 1-phosphate; SK, sphingosine kinase; SM, sphingomyelin; SMS, sphingomyelin synthases; Sph, sphingosine; SPL, S1P lyase; SPNS2, protein spinster homolog 2; SPP, S1P phosphatase; SPT, serine palmitoyltransferase.

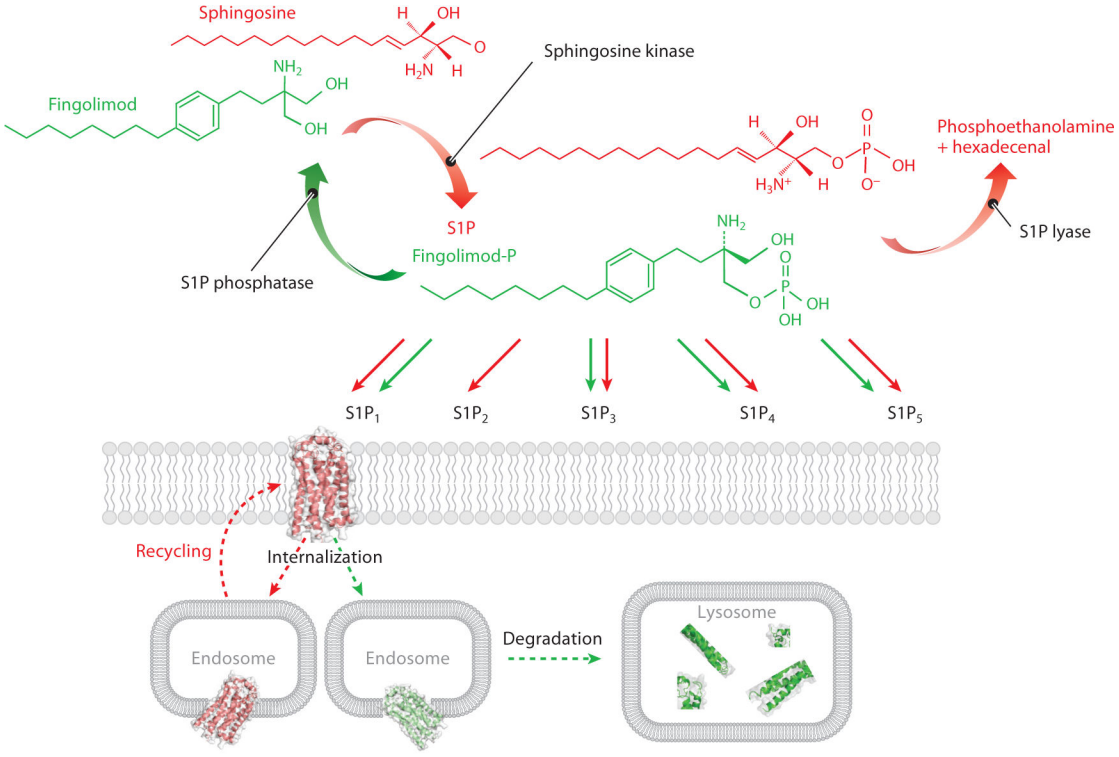

Figure 6.

Functional antagonism of S1P1 by fingolimod-P. Sphingosine kinase phosphorylates both sphingosine and fingolimod to generate S1P and fingolimod-P, respectively. Fingolimod-P can bind with S1P1,3,4,5. Both S1P and fingolimod-P induce S1P1 internalization. S1P induces internalization of S1P1 and endosomal recycling to the cell surface, whereas fingolimod-P induces irreversible internalization of S1P1 by ubiquitinylation and proteasomal degradation, resulting in a loss of cell surface S1P1 expression. Abbreviations: fingolimod-P, fingolimod-phosphate; S1P, sphingosine 1-phosphate.

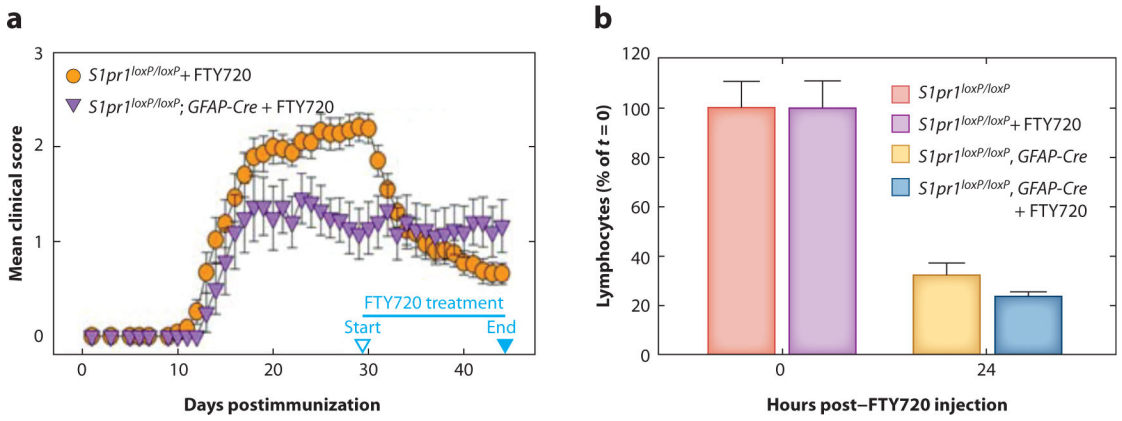

Figure 7.

Astrocyte-specific effects of FTY720 in the mouse model of multiple sclerosis (EAE). (*a*) Astrocyte-specific S1P1-KO (*S1pr1loxP/loxP*, *GFAP-Cre*) mice displayed decreased EAE clinical scores and were refractory to FTY720 exposure at the start (*open triangle*) and end (*closed triangle*) of FTY720 treatment. (*b*) Normal blood lymphocyte responses to FTY720 treatment in astrocyte-specific S1P1-KOs, as compared to wild-type controls. Abbreviations: EAE, experimental autoimmune encephalomyelitis; KO, knockout; S1P, sphingosine 1-phosphate. Figure adapted with permission from Reference 75.

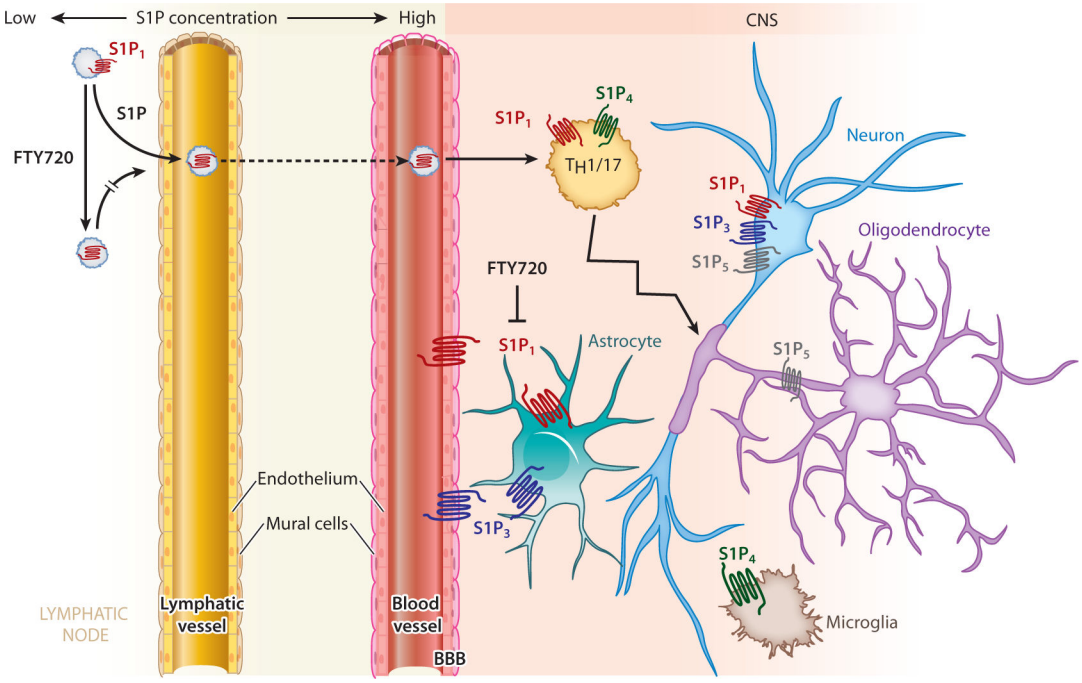

Figure 8.

Mechanism of action of fingolimod (FTY720) in multiple sclerosis. T cells expressing S1P1, sensing differences in the S1P concentration present between tissues and circulatory fluids, egress from the secondary lymphoid organs to the blood and lymph. FTY720 suppresses S1P1 signaling through functional antagonism, resulting in the sequestration of lymphocyte subpopulations. FTY720 also alters astrocyte function and may affect oligodendrocyte function via S1P5. Abbreviations: BBB, blood-brain barrier; CNS, central nervous system; S1P, sphingosine 1-phosphate.

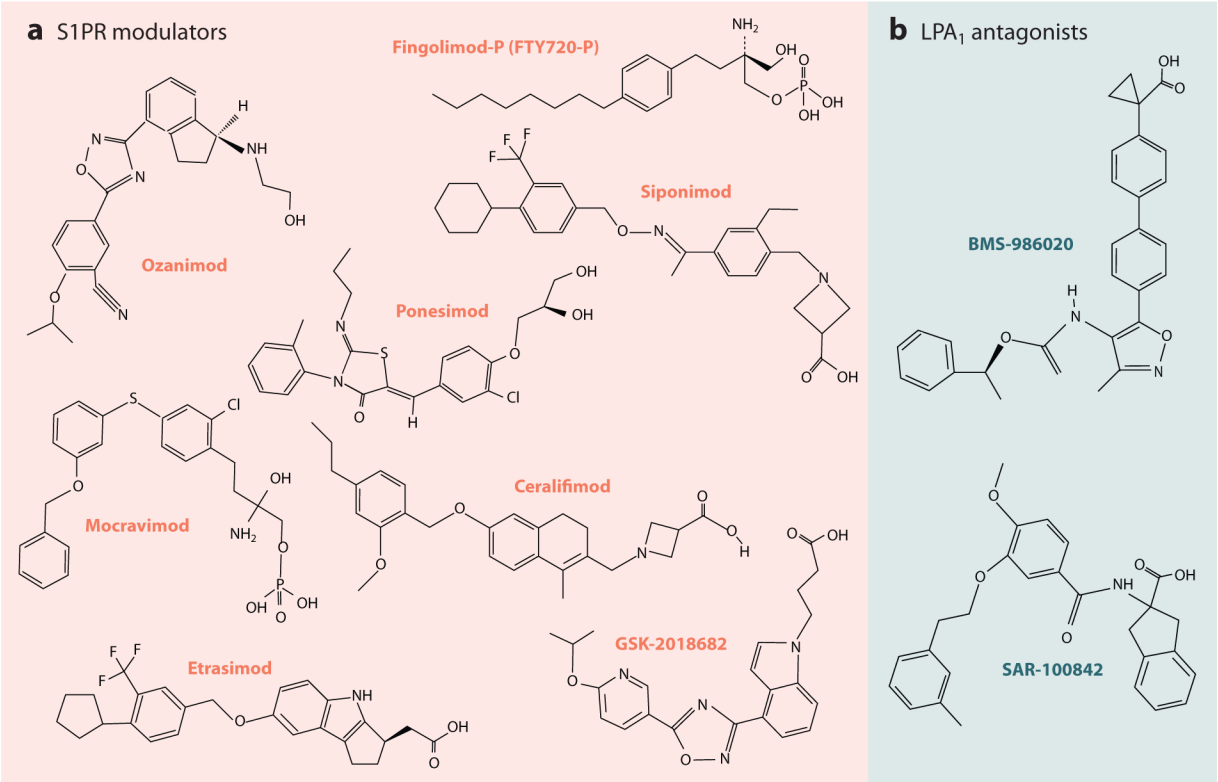

Figure 9.

Chemical structures of clinically relevant (*a*) S1PR modulators and (*b*) LPA1 antagonists. The IUPAC names for each compound are as follows: fingolimod-P (FTY720-P), [2-amino-2-(hydroxymethyl)-4-(4-octylphenyl)butyl] dihydrogen phosphate (https://www.novartis.com/); ozanimod (RPC1063), 5-[3-[(1*S*)-1-(2-hydroxyethylamino)-2,3-dihydro-1H-inden-4-yl]-1,2,4-oxadiazol-5-yl]-2- propan-2-yloxybenzonitrile (https://pubchem.ncbi.nlm.nih.gov/compound/52938427); siponimod (BAF312), 1-[[4-[(*E*)-*N*-[[4-cyclohexyl-3-(trifluoromethyl)phenyl]methoxy]-*C*-methylcarbonimidoyl]-2-ethylphenyl]methyl]azetidine-3-carboxylic acid (www.novartis.com/); ponesimod (ACT-128800*)*, (5*Z*)-5-[[3-chloro-4-[(2*R*)-2,3-dihydroxypropoxy]phenyl]methylidene]-3-(2-methylphenyl)-2-propylimino-1,3-thiazolidin-4-one (https://www1.actelion.com/); ceralifimod (ONO-4641*)*, 1-[[6-[(2-methoxy-4-propylphenyl)methoxy]-1-methyl-3,4-dihydronaphthalene-2-yl]methyl]azetidine-3-carboxylic acid (https://www.emdgroup.com/en); mocravimod (KRP-203), 2-amino-2-[2-[2-chloro-4-(3-phenylmethoxyphenyl)sulfanylphenyl]ethyl]propane-1,3-diol (http://www.kyorin-pharm.co.jp/en/); etrasimod (APD334), 2-[(3*R*)-7-[[4-cyclopentyl-3-(trifluoromethyl)phenyl]methoxy]-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl]acetic acid (http://www.arenapharm.com/); GSK-2018682, 4-[4-[5-(5-chloro-6-propan-2-yloxypyridin-3-yl)-1,2,4-oxadiazol-3-yl]indol-1-yl]butanoic acid (https://www.gsk.com/); BMS-986020, 1-[4-[4-[3-methyl-4-[[(1*R*)-1-phenylethoxy]carbonylamino]-1,2-oxazol-5-yl]phenyl]phenyl]cyclopropane-1-carboxylic acid (https://www.bms.com/); and SAR-100842, 2-[[4-methoxy-3-[2-(3-methylphenyl)ethoxy]benzoyl]amino]-1,3-dihydroindene-2-carboxylic acid (https://www.sanofi.com/en/). Abbreviations: fingolimod-P,

fingolimod-phosphate; IUPAC, International Union of Pure and Applied Chemistry; LPA, lysophosphatidic acid; S1P, sphingosine 1-phosphate; S1PR, S1P receptor.

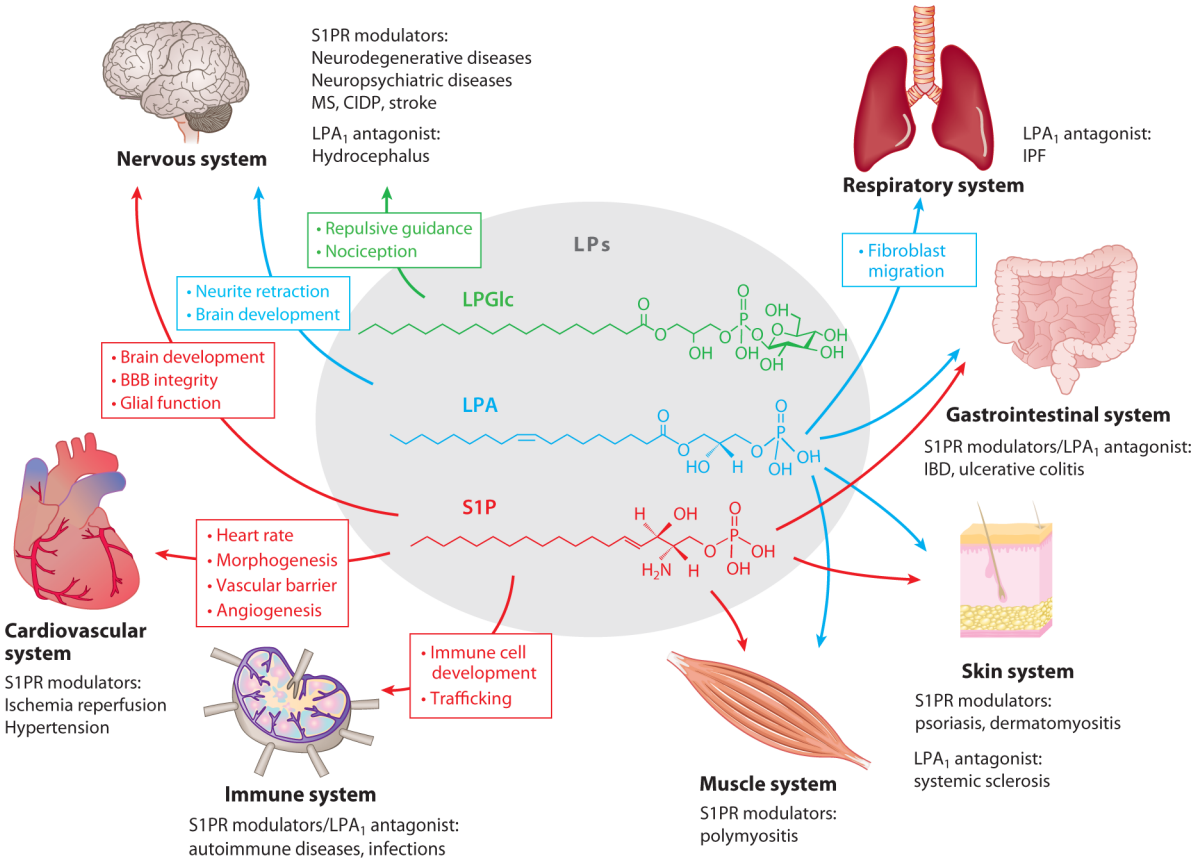

Figure 10.

LP receptor functions and diseases in organ systems. LP receptors function in different organs and potential therapeutic areas. Receptors and metabolic pathways of LPs such as LPGlc, LPA, and S1P are attractive drug targets for neurological and immunological diseases including MS, CIDP, IPF, and IBD. Brain disorders include a range of potential opportunity areas from fetal hydrocephalus through Alzheimer's disease (9, 10, 21). Abbreviations: BBB, blood-brain barrier; CIDP, chronic inflammatory demyelinating polyneuropathy; IBD, inflammatory bowel disease; IPF, idiopathic pulmonary fibrosis; LP, lysophospholipid; LPA, lysophosphatidic acid; LPGlc, lysophosphatidyl glucose; MS, multiple sclerosis; S1P, sphingosine 1-phosphate; S1PR, S1P receptor.